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A strategy for producing predicted polymorphs: catemeric carbamazepine form V†

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A computationally assisted approach has enabled the first catemeric polymorph of carbamazepine (form V) to be selectively formed by templating the growth of carbamazepine from the vapour phase onto the surface of a crystal of dihydrocarbamazepine form II.

Why are more polymorphs of organic molecules predicted than are observed experimentally?[1,2] Either predictive methods overestimate the true potential for polymorphism or experimental polymorph screens do not sample the appropriate nucleation and growth conditions required to encounter all forms. This question is of particular significance given the importance of controlling solid-state structure in many chemical industries, either as a means of optimizing a material's properties[3] or to prevent the unexpected appearance of a new form during the development of a production process.[4] A considerable challenge therefore is to improve upon established approaches to solid form discovery[5–7] to select a specific desired crystal structure from the predicted crystal energy landscape (*i.e.* those computed to be thermodynamically feasible). The development of such computationally-assisted crystal engineering strategies[8,9] would move experimental crystal form discovery beyond the traditional reliance on empiricism and serendipity. Here we demonstrate how computed crystal energy landscapes can be used in this manner, specifically, to design a method for producing a specific new polymorph (form V†) of the anti-epileptic drug carbamazepine (CBZ, Fig. 1).

CBZ has over 50 reported forms including 4 polymorphs.[10–15] The structures of CBZ I, II, III and IV are all based on a hydrogen-bonded dimer motif[13] and despite extensive experimental polymorph searches involving diverse approaches,[12,15–19] a pure catemeric form of this molecule has never been reported. The strategy leading to the discovery of CBZ V is based on the selection of an orthorhombic polymorph (form II) of the CBZ analogue DHC[20] (Fig. 1) as a structural template for a predicted, though unobserved, catemer-based form of CBZ (see ESI).[12,21]

In an effort to obtain insights into the crystallization of CBZ itself, an extended experimental and computational investigation into physical form diversity in CBZ[12,21] and the related molecules DHC,[22,23] CYH[24] and CYT[25] was carried out. The computed lattice energy landscapes of each molecule[4,12,23] show that structures based on either hydrogen-bonded dimer or catemer motifs are thermodynamically feasible in every case. The experimental investigations, starting from an automated solution crystallization screen, produced several new polymorphs[21–25] revealing close structural relationships between the experimentally determined structures shown in Fig. 2.

To further explore the isostructural relationships that emerged, improved lattice energy calculations[26] were carried out in which the 4 molecules were substituted in turn into each of the 8 distinct experimental lattices observed across the series (Fig. 3, details in ESI). The simulated structure corresponding to CBZ substituted in DHC II (*i.e.* CBZ V) is relatively low on the lattice energy plot and comparable in stability with the previously observed forms (Fig. 3).

As suggested by these calculations, CBZ V was successfully obtained by templating growth of CBZ from the vapour phase onto the surface of a DHC II crystal. 50 mg of CBZ III was placed in a 10 mL glass vial and a single crystal of DHC II was attached to a copper wire and suspended 1–2 cm above the CBZ. The sealed vial was placed onto a hot-plate at 125 °C for 24–48 h. CBZ crystals formed by reverse sublimation onto the surface of the seed and these crystals were removed and identified by single-crystal X-ray diffraction. Crystals that grew on the seed always formed on the smallest edge faces of the crystal (Fig. 4) whilst those that grew on the wire or

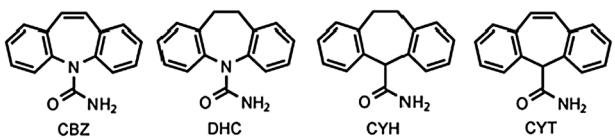

Fig. 1 CBZ and the related molecules 10,11-dihydrocarbamazepine (DHC), cyheptamide (CYH) and cytenamide (CYT).

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† Electronic supplementary information (ESI) available: Crystal structure parameters for DHC II, the predicted form and CBZ form V; X-ray diffraction details for CBZ form V and computational method for lattice energy calculations. CCDC 791775. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc11634g

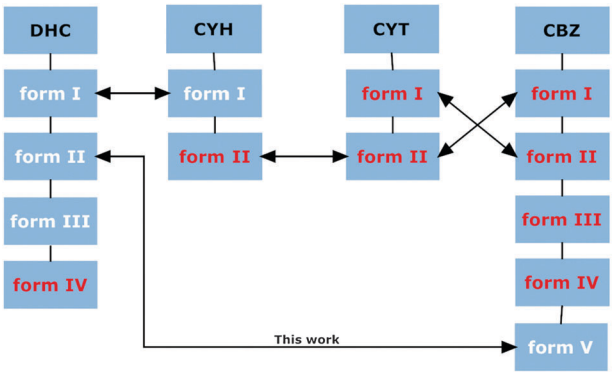

Fig. 2 Relationships between experimental forms of DHC, CYH, CYT and CBZ. White and red labels correspond to catemer- and dimer-based structures respectively; black arrows identify isostructural relationships, including that between DHC II and CBZ V.

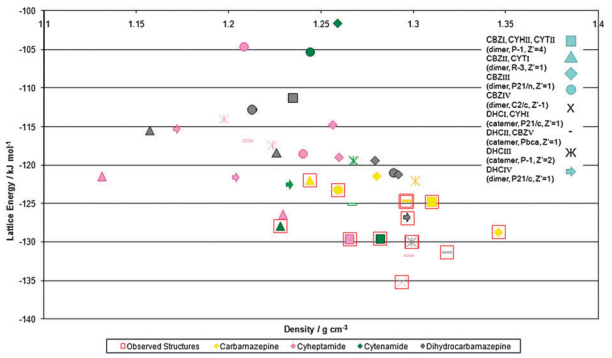

Fig. 3 Lattice energy substitution calculations for CBZ, CYT, CYH and DHC in the 8 distinct crystal structure types observed experimentally (Fig. 2). The colour of each symbol denotes the molecule (CBZ—yellow, CYH—pink, CYT—green and DHC—grey) and the symbol represents the lattice. Each substitution that matches an observed form is highlighted as an open box, with CBZ V in a double red box.

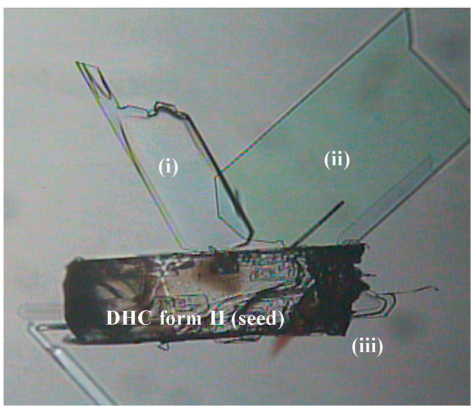

Fig. 4 DHC II seed crystal with thin plates of CBZ V (i–iii) emerging from the edge faces.

inside walls of the vial were either CBZ I or III. The crystal structure of form V is catemeric (Fig. 5)‡ and is isostructural with DHC II and the simulated CBZ structure (see ESI).

The formation of this specific CBZ polymorph, achieved by combining experimental and computational studies of polymorphic diversity in related molecules, has thus verified

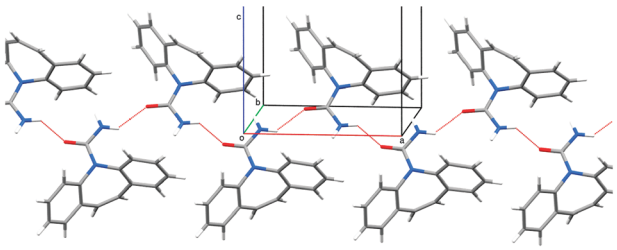

Fig. 5 Single crystal structure of CBZ V showing the catemeric hydrogen bonded motif extending in the direction of the *a*-axis.

the initial computational predictions that catemeric forms of CBZ are feasible. Further work on this and other molecular families is required to assess the general transferability of this computationally-assisted approach to polymorph screening by lattice energy calculations on isomorphous structures and to define the templating mechanism in detail.

Form V CBZ represents a significant advance in polymorph discovery and control in that it did not result from the facile extension of experimental crystallization search space for the molecule, but rather by computer-aided exploration of the polymorphs of related molecules to find a template. This approach of combining crystal energy landscape prediction, experimental screening, and lattice energy substitution calculations illustrates a strategy to increase the probability that all practically important long-lived polymorphs are discovered. In so doing, these methods offer a new paradigm in the control and selection of solid-state properties of pharmaceuticals and other speciality chemicals.

A predicted catemeric polymorph of CBZ has been produced experimentally by exploiting the 3D similarity between computed and experimental structures of closely related molecules to find a solid-state template. The fact that form V CBZ has not been observed before, despite extensive polymorph screening, emphasizes the need for caution in concluding that unobserved thermodynamically feasible structures cannot appear. In the case of CBZ at least, it would seem that previous experimental searches provided insufficient coverage of the experimental crystallization space to allow the formation of this polymorph.

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Notes and references

‡ Diffraction data were collected at 123 K from a CBZ V crystal measuring 0.12 × 0.08 × 0.04 mm using Cu-Kα radiation (λ = 1.54180 Å), measured reflections = 5416, independent reflections = 2140, θ_{max} = 67.96, R_{int} = 0.0624, 171 parameters, R = 0.045 (based on F and 1219 data with $F^2 > 2\sigma(F^2)$), R_w = 0.1018 (based on F^2 and all 2140 unique reflections), S = 0.824. Orthorhombic, space group *Pbca*, unit cell parameters a = 9.1245(5), b = 10.4518(5), c = 24.8224(11) Å, volume = 2367.2(2) Å^3; Z = 8, ρ_c = 1.326 g cm^{-3}, $C_{15}H_{12}N_2O$, Mr = 236.3.

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